Acute Cardiac Unloading and Recovery

Proceedings of the first annual Acute Cardiac Unloading and REcovery (A-CURE) symposium held on 26th August 2016 in Rome, Italy

Session summaries by Katrina Mountfort, Medical Writer, Radcliffe Cardiology

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Foreword

Welcome to this special supplement of Interventional Cardiology Review. This supplement is devoted to the proceedings of the first annual Acute Cardiac Unloading and REcovery (A-CURE) symposium, which was held on 26 August 2016 in Rome, Italy. This 1-day meeting brought together experts from a number of disciplines – including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists and biomedical engineers – to discuss the science behind and clinical application of acute cardiac unloading. Over 100 physicians, clinical and preclinical researchers, basic researchers, medical students, post-doctoral scientists and graduate students from 21 different countries were in attendance.

The growing global heart failure patient population poses clinical, economic and social challenges and there is no clear line of sight to a sustainable solution. The goal of the A-CURE meeting was to share cutting-edge, cross-discipline basic and clinical research, looking at acute cardiac unloading as a therapeutic platform for the prevention of heart failure and the development of therapies aimed at heart muscle recovery. One of the focuses of this meeting was on advancing the paradigm shift currently underway in the management of myocardial ischaemia–reperfusion injuries. Although early coronary intervention has reduced the acute mortality in myocardial infarction (MI), the late development of heart failure is increasing at an alarming rate. For the first time, acute cardiac unloading within the clinic has been made technically feasible by the development of percutaneously-inserted ventricular assist devices (VADs) such as the Impella® (Abiomed) and the TandemHeart® (CardiacAssist Inc). These devices mechanically unload the heart and reduce myocardial oxygen consumption. Clinical and preclinical investigations from independent laboratories over the past decade have routinely demonstrated that acute unloading has beneficial impacts when treating acute MI and other aetiologies of acute heart failure. For the first time, the A-CURE symposium brought together leading researchers in the field of acute unloading to present their current work and generate open scientific discussions in a public forum.

This supplement features a number of presentations describing the basic science underlying acute unloading of the heart, its clinical applications, and the opportunities in and challenges of performing clinical trials. The morning’s presentations were largely devoted to preclinical studies and the basic science underlying mechanical unloading. The meeting began with an overview from Eugene Braunwald, one of the most renowned figures in the field of cardiology. Daniel Burkhoff presented the basic science behind acute ventricular and myocardial unloading. Next, Kenji Sunagawa described vagal nerve stimulation, another approach to myocardial protection that has been combined successfully with mechanical unloading in animal models. Navin Kapur explored further the concept of mechanical unloading, discussing the mechanism of cardioprotection at the cellular level. In addition, Dr Kapur described a number of fascinating studies demonstrating that initially reducing left ventricular work and delaying coronary reperfusion may limit myocardial injury in acute MI. A member of Dr Kapur’s research team, Michele Esposito, was the winner of the Young Investigator Scholarship presented by the A-CURE Working Group. Dr Esposito described her study demonstrating that primary unloading causes a change in gene expression within the infarct zone that initiates a number of cardioprotective processes during acute MI. To close the morning session, Patrick Hunziker shared insights from his considerable experience of implanting Impella VADs.

The afternoon’s presentations had a stronger focus on clinical and practical studies. The keynote speaker, Joseph Hill, discussed the global health and economic burden of heart failure, as well as describing the factors affecting myocardial plasticity. Mark Anderson presented a surgeon’s perspective on cardiac unloading and myocardial recovery. William O’Neill presented data from the catheter-based VAD Registry™, a global observational clinical registry designed to monitor patient safety and real-world outcomes of patients supported with the Impella device. James Udelson discussed the practical difficulties of designing clinical trials to test the efficacy and safety of left VADs in a patient population where event rates are low. Michael Cohen discussed the benefits of post-conditioning at the time of reperfusion in acute MI. Ryan Tedford described the use of mechanical support for right-sided and biventricular failure. Finally, Derek Hausenloy identified other opportunities, in addition to unloading, for reducing infarct size following MI. Dr Kapur closed the meeting by acknowledging that the day had been ground-breaking in involving such a diversity of expertise from multiple disciplines.

Interventional Cardiology Review would like to thank all expert reviewers who contributed towards this edition. A special thanks goes to our editorial board for their continuing support and guidance. We hope that you find this supplement informative and interesting.
Acute MI to Heart Failure: the Past, the Present and the Future

Presented by Dr Eugene Braunwald

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Dr Eugene Braunwald is one of the most eminent figures in modern cardiology and has authored more than 1,000 peer-reviewed publications. His work has increased current understanding of congestive heart failure, coronary artery disease and valvular heart disease. Among his notable works are the Thrombolysis in Myocardial Infarction studies, which elucidated the pathophysiology of acute myocardial infarction. He is also responsible for Braunwald’s Heart Disease, the most widely read textbook of cardiology in the world.

Dr Braunwald began by discussing his early work on the determinants of myocardial oxygen consumption. The idea that early reduction of myocardial oxygen demands and improvement of coronary perfusion might reduce infarct size dates back to the early 1970s. This concept was advanced further in 1976 with the first publication of coronary reperfusion after coronary thrombolysis, and in 1981 when it was proven that thrombolytic reperfusion salvaged myocardial tissue.

These findings led to the establishment of the Thrombolysis in Myocardial Infarction (TIMI) study group by the National Institutes of Health in 1985. Among this group’s most important developments was the TIMI Risk Score, which assesses the risk of death and ischaemic events in patients experiencing unstable angina. The next major advance in the relationship between acute myocardial infarction (AMI) and heart failure (HF) was in 1987, when Pfeffer et al. found that the haemodynamic profile of chronic HF secondary to myocardial infarction (MI) could be pharmacologically altered in rats, but the improvements were significantly diminished in hearts with large infarcts. This finding led to the first report of post-AMI cardiac remodelling in 1990. These findings established the pathophysiological basis for the progression to HF in patients with AMI and were a key milestone toward the development of reperfusion strategies, including primary percutaneous coronary intervention (PCI).

A 2013 study found that in Medicare beneficiaries, hospitalisation for HF during the first year after discharge compared to those without CS, and survivors of AMI-CS had a higher risk of death and/or hospitalisation during the first year after discharge compared to those without CS, and that the risk was highest in the early post-discharge period (first 60 days). After this time, the prognosis was similar in patients with or without CS.

The failure of pharmacological treatments to maintain adequate perfusion and to prevent irreversible end-organ failure in many patients with CS has led to attempts to improve outcomes by mechanical circulatory support (MCS) devices. Until recently, initiation of MCS with an intra-aortic balloon had a class I recommendation for the treatment for CS-AMI and had become widely used. However, a 2012 study found that use of the intra-aortic balloon did not
reduce 30-day mortality in patients with MI and CS. A 2014 study showed that early use of the Impella 2.5 prior to PCI was associated with more complete revascularisation and improved survival in the setting of refractory CS-AMI. The Impella 5.0 has also been studied for CS resulting from AMI, dilated cardiomyopathy and postcardiotomy cardiac failure: this has demonstrated impressive outcomes in terms of mortality (see Figure 1). Furthermore, following removal of the Impella, patients’ left ventricular ejection fraction improved significantly (p<0.001) when compared to baseline (see Figure 2).

As a result of these findings, the 2015 clinical expert consensus statement on the use of percutaneous MCS devices in cardiovascular care stated that percutaneous MCS provides superior haemodynamic support compared to pharmacological therapy. The guidelines also stated that in profound CS, MCS using intra-aortic balloon is less likely to provide benefit than continuous flow pumps. Dr Braunwald discussed the importance of early placement of an appropriate MCS as being key in patients in CS who fail to stabilise or quickly show improvement after initial intervention. Furthermore, MCS may be considered for patients undergoing high-risk PCI.

Dr Braunwald emphasised the need to develop strategies to reduce reperfusion injury, which is a major contributor to the final myocardial infarct size. There is also a need to reduce myocardial oxygen demands and to initiate early pharmacological treatment to reduce ventricular size and diminish wall stress. Secondary prevention of recurrent AMI is also important. This should involve intensive reduction of low-density lipoprotein through the use of proprotein convertase subtilisin/kexin type 9 inhibitors to reduce recurrent AMI.

Dr Braunwald concluded by emphasizing that early application of these new MCS devices is needed in AMI-CS and acute, decompensated HF. Brief, temporary MCS should be applied for a longer period and may become a bridge to surgically-implanted durable left ventricular assist devices, biventricular assist devices, cardiac transplantation and recovery.


The Science Behind Acute Ventricular and Myocardial Unloading
Presented by Daniel Burkhoff
Cardiovascular Research Foundation and Columbia University, New York, USA

Dr Burkhoff is an Associate Professor of Medicine at Columbia University, Division of Cardiology. He has authored more than 200 peer-reviewed publications. He is a world expert in pressure-volume relationships in the heart.

Dr Burkhoff began his presentation by outlining clinical goals in the setting of acute myocardial insult, including myocardial infarction, cardiogenic shock and chronic heart disease. These goals include myocardial salvage to minimise the amount of myocyte loss and to prevent, or at least limit, myocardial and ventricular remodelling with the aim of maintaining normal left ventricular (LV) size and function. Another important goal is to improve both short- and long-term survival: this is poor in patients presenting with cardiogenic shock in the first 30 days, and the risk of death persists over several years. The major physiological goals are to achieve a normal haemodynamic profile in terms of cardiac output, mean arterial pressure, central venous pressure and pulmonary capillary wedge pressure. However, these approaches do not specifically target myocardial injury in acute myocardial infarction (AMI). It is also
important to reduce LV preload pressure to prevent acute stretch of the ventricular wall and subsequent remodelling, and to minimise myocardial oxygen consumption. Dr Burkhoff emphasised how myocardial oxygen consumption – the major contributors to which are heart rate, LV contractility and myocardial mechanical work (pressure–volume work) – may be influenced by cardiac unloading.

An important concept underlying the lack of success of pharmacological interventions such as inotropes in the treatment of AMI is that these approaches increase the power expenditure of the heart, thereby increasing the stress placed on the organ. This contrasts with what occurs in acute LV unloading. Acute cardiac unloading is defined as the reduction of total mechanical power expenditure (as opposed to work) of the ventricle, which correlates with reduction in myocardial oxygen consumption and the haemodynamic forces that lead to ventricular remodelling.

The use of LV support has been an area of active clinical research since the mid-1990s. In 2003, Meyns et al. first reported that the use of an early version of the Impella® (Abiomed) device reduced infarct size in animal models. This study also found that the area of infarct is related to oxygen consumption during ischaemia and reperfusion. The index of myocardial work that correlates most closely with myocardial oxygen consumption is known as the pressure–volume area (PVA). This is the sum of the stroke work and the potential energy, i.e. the energy that is stored in the myocardial filaments after contraction rather than being released as external work. Heart rate and contractility are also important determinants of myocardial oxygen consumption. There is a linear relationship between PVA and myocardial oxygen consumption, and this relationship increases with increased contractility. It is worth noting that there is still a substantial amount of oxygen consumption in the absence of mechanical work, which is needed for the basal metabolism of cells as well as the processes of calcium cycling responsible for contractile activation. Increasing contractility increases both calcium cycling and oxygen consumption. Heart rate has a significant impact on the relationship between oxygen consumption and PVA because each contraction involves the release of calcium and oxygen consumption, increasing the intercept and slope (see Figure 1).

The physiological goals of myocardial unloading may be achieved by various means. These include pharmacological interactions involving ionotropic agents or vasopressors and the use of mechanical circulatory support (MCS) devices. The use of ionotropes increases heart rate, contractility and PVA, while the use of vasopressors increases total peripheral resistance. Since the resulting increase in heart rate has a detrimental effect on oxygen consumption, if cardiac recovery is a therapeutic goal the use of these agents should be minimised.
Dr Burkhoff next compared the available MCS devices, including the intra-aortic balloon pump, the shortcomings of which were discussed in Dr Braunwald’s presentation. Another device, the TandemHeart™ (CardiacAssist Inc), is a left ventricular assist device that pumps blood from the left atrium to the aorta. Implantation requires trans-septal puncture, which may be a challenging procedure in an acute setting. A third MCS, peripheral extracorporeal membrane oxygenation (ECMO), is an intervention that draws blood from the vena cava and pumps it into the descending aorta, but this increases the LV afterload. The Impella ventricular support device aspirates blood from the left ventricle into the aorta. Since these four devices take blood from different regions of the heart, they have different effects on LV energetics. Each device has a characteristic impact on the pressure–volume loop.

While the patient is on peripheral ECMO support, the left ventricle must eject blood through the aorta. The ventricular end diastolic pressure will therefore rise to accommodate the increase in arterial pressure resulting from ECMO support. This results in an increase in the preload on the ventricle, and as a consequence the PVA and oxygen consumption increase. This is energetically unfavourable to the heart. Furthermore, the increased diastolic ventricular pressures can actually promote detrimental myocardial remodelling.

The Impella device has the opposite effect on myocardial energetics. It functions by aspirating blood directly from the ventricle into the aorta. As a result, the pressure–volume loop shifts left towards a lower volume, end diastolic pressure is reduced and PVA decreases. Since the reduction in the PVA means a reduction in myocardium oxygen demand, this effect is favourable (see Figure 2). Also important is the concept of LV–aortic uncoupling. If sufficient unloading is provided, the maximum pressure generation of the ventricle is reduced. If this pressure falls below the mean arterial pressure, the aortic valve will not open and blood is no longer ejected from the ventricle, thereby minimising the mechanical work of the heart. In this way, LV–aortic pumping alone maintains sufficient cardiac output and aortic pressure is uncoupled from LV function. Thus, acute unloading can greatly decrease myocardial energy consumption and the haemodynamic forces that drive ventricular remodelling processes. This is contrary to pharmacological interventions such as inotropes, that increase myocardial energy consumption and exacerbate unfavourable haemodynamic forces. The use of the Impella can thus potentially replace inotropes and avoid these detrimental effects, all while achieving physiological goals.

Dr Burkhoff discussed the important concept of the dose dependence of unloading, i.e. the relationship between the degree of support and degree of unloading. It is important to distinguish between partial support/full unloading and full support/full unloading, and to understand that unloading and support are not necessarily equivalent (see Figure 3). Partial support and partial unloading occurs when the heart continues to provide some of the cardiac output while the device provides the rest. In this scenario, the aortic valve still opens and closes and the heart ejects blood. In full support/partial unloading the entire cardiac output is provided by the MCS. In this scenario, the entire cardiac output is provided by the device, the heart is not ejecting blood and the aortic pressure is uncoupled from ventricular function. Oxygen consumption is reduced. During full support/full unloading, however, the volume unloading of the ventricle is not maximised. Maximum reduction in ventricular volume and oxygen consumption is achieved during full support/full unloading. In this scenario, mechanical support is increased such that the ventricular preload (volume) is minimised. This shifts the pressure–volume relationship further leftward, minimising the PVA.

In summary, with acute haemodynamic compromise in the setting of myocardial insult, the aims are to restore normal haemodynamics, minimise LV filling pressure, minimise oxygen consumption, prevent remodelling and enhance myocardial salvage. Unlike MCS, pharmacological approaches increase oxygen consumption and increase the load on the left ventricle. Different methods of MCS have different effects on haemodynamics and myocardial energetics. Venous-to-aortic devices do not unload the heart or reduce oxygen consumption, whereas left ventricle-to-aorta devices do. The latter also uncouple the left ventricle and aorta, allowing for unloading of the left ventricle while restoring arterial blood pressure and flow.


Neuromechanical Unloading for Acute Myocardial Infarction

Presented by Kenji Sunagawa

Center for Cardiovascular Medicine, Kyushu University, Fukuoka, Japan

Kenji Sunagawa is the founder and Professor of the Center for Disruptive Cardiovascular Medicine at Kyushu University, Fukuoka, Japan. He joined the cardiovascular group at the Department of Biomedical Engineering, Johns Hopkins University, in 1978 and helped establish the concept of the pressure–volume relationship of the heart.

Dr Sunagawa began by highlighting the concept of ischaemia as an imbalance between oxygen supply and demand. Previous interventions have focused on increasing oxygen supply, but this approach may be insufficient to improve outcomes. Mechanical
Neuromechanical Unloading for Acute Myocardial Infarction

unloading has the effect of decreasing oxygen demand and can be considered ‘functional reperfusion’. However, while it is possible to dramatically reduce myocardial oxygen consumption by the use of left ventricular assist devices (LVADs), Dr Sunagawa is exploring additional complementary approaches to further reduce myocardial oxygen demand to provide cardiac protection.

Another approach to myocardial protection is vagal nerve stimulation (VNS). It is well established that VNS has anti-ischaemic effects. These are mediated by complex mechanisms, including heart rate reduction, anti-adrenergic effects and anti-inflammatory effects (see Figure 1). Various preclinical studies have demonstrated that VNS results in marked reductions in infarct size following acute myocardial infarction. Since VNS removes acute myocardial infarction-induced neuromechanical and inflammatory stress, it has been termed neural unloading.

This technique of neural unloading has recently been investigated in conjunction with mechanical unloading. In order to stimulate the vagal nerve in a minimally invasive manner, a catheter with electrodes was inserted into the superior vena cava of a dog. This rapidly decreased the heart rate and, as a consequence, reduced myocardial oxygen consumption by >50%.

In order to investigate the impact of this investigation on infarct size, an ischaemia reperfusion model was created in 24 dogs by occluding the left anterior descending coronary artery for 180 minutes and then reperfusing. Left ventricular unloading was performed with the impella CP® (Abiomed) device. Transvascular VNS was performed with a pacing catheter in the superior vena cava. The neuromechanical unloading started 90 minutes after the onset of ischaemia and ended 60 minutes after reperfusion. Dogs were then assigned to one of four groups: ischaemia reperfusion (n=7), LVAD (n=6), VNS (n=4) and LVAD plus VNS (n=5). One month after the intervention, the infarct size and cardiac function were compared. The use of LVAD plus VNS reduced the infarct size by >70% (p<0.05; see Figure 2).

This combined strategy of mechanical and neural unloading is clearly a powerful intervention and provides almost complete ventricular support. A key factor underlying the success of this approach is the heart rate reduction provided by the combined technique. It has therefore been hypothesised that the combination of mechanical circulatory support and pharmacological heart rate reduction may be beneficial in acute myocardial infarction. The Iγ inhibitor ivabradine is a bradycardic agent; ongoing studies are investigating the combination of ivabradine and LVADs on oxygen consumption in acute myocardial infarction.

Dr Sunagawa concluded that the combination of LVAD and VNS synergistically reduces infarct size beyond that observed by LVAD unloading alone, preserves left ventricular function, and prevents heart failure in the long term. In order to establish total unloading as a treatment for acute myocardial infarction in humans, the development of higher flow percutaneous pumps is essential. In addition to this, in order to maximise the beneficial impacts, the simultaneous regulation of LVAD and VNS needs to be optimised in further studies.

References:
Dr Kapur began considering the reasons for the paradigm shift in interventional therapy targeting ischaemia-reperfusion injuries. The past decade has seen a transition in outcomes for patients presenting with acute myocardial infarction (AMI). A cohort study \((n=7,733)\) of older patients with first myocardial infarction (MI) showed that although the in-hospital mortality decreased by 28 % over 5 years, the 5-year incidence of heart failure increased by 25 %.\(^1\) The burden of ischaemic heart failure has become the new challenge in the treatment of MI. The current treatment paradigm focuses on rapid reperfusion to limit myocardial damage. However, the significant improvement in door-to-balloon times (DBTs) in the past 10 years (to <90 minutes) has had no impact on mortality rates, which remain at around 7 % for patients with anterior MI and 27 % for those with cardiogenic shock.\(^2\)

Dr Kapur maintained that reperfusion has become a double-edged sword: while prolonged ischaemia can cause substantial injury, restoration of perfusion to the ischaemic heart can exacerbate tissue damage. DBTs have decreased because of the adage that ‘time is muscle’. When a coronary vessel becomes occluded, the acute ischaemic insult activates a process within cardiac myocytes involving a decrease in oxidative phosphorylation and adenosine triphosphate synthesis, which leads to a decrease in intracellular pH due to calcium influx and lactate elevations within these myocytes. This can lead to downstream effects on coronary function whereby the mitochondria become dysfunctional, generate reactive oxygen species and may even burst, resulting in cell death and necrosis. The current treatment of reperfusion creates a feed-forward mechanism, inducing further mitochondrial and oxidative damage. However, the body has an inherent counter-regulatory mechanism. First, at the endothelial level, endogenous tissue plasminogen activator attempts to autolise thrombotic occlusions. At the cardiac myocyte level, there is a significant increase in salvage kinase activation, largely of extracellular-regulated kinase and protein kinase B. These kinases initiate an antiapoptotic signalling pathway designed to counteract the effect of reperfusion injury.

It is clear that many barriers exist to cardioprotective approaches and numerous drug trials attempting cardioprotection in the setting of AMI have failed. The critical barriers to success have been the mandate for rapid coronary reperfusion (i.e. DBT), the inability to target multiple cascades affecting reperfusion injury and the challenges of managing haemodynamic instability. A recent editorial critically appraised current approaches and asked the question: is it time to give up on cardioprotection?\(^3\) Pre-ischaemic conditioning is not feasible, post-ischaemic conditioning has limited feasibility, and studies have been inconclusive. Remote ischaemic conditioning has been associated with limited efficacy and findings have not been conclusive. There is therefore a need for new approaches to cardioprotection in AMI.

A key theme of the A-CURE meeting is the novel paradigm of limiting myocardial ischaemia by minimising oxygen demand then restoring oxygen supply, a procedure that has been termed functional reperfusion. Insights from the surgical management of ST-elevation MI have taught us that a procedure beginning with unloading (cardiopulmonary bypass) followed by reperfusing ischaemic myocardium results in the restoration of coronary function.\(^4\) However, this surgical mindset contrasts with the interventional approach and has not been adopted due to our limited ability to unload the myocardium without major cardiac surgery.

Over the past decade, a number of percutaneous mechanical circulatory support devices have become available (see Figure 1) and these have been described in previous presentations. The earliest work with intra-aortic balloon pumps showed that initiating mechanical support during infusion and reperfusion can reduce infarct size.\(^5\) This model is limited, however, in that the device is activated at the onset of ischaemia and remains on throughout reperfusion, so it is hard to translate to clinical use. Further studies have used axial-flow pumps (Impella\(^\text{®}\), Abiomed) as a direct left ventricular (LV) loading mechanism and focussed not only on activation timing but also investigated the concept of total and partial unloading. An early study in sheep found that if Impella is activated during reperfusion alone, the degree of unloading correlates with a reduction in infarct size.\(^6\)

Dr Kapur’s team has been investigating the novel hypothesis that initially reducing LV work and delaying coronary reperfusion may limit myocardial injury in AMI. The choice of delayed reperfusion was driven by necessity in order to replicate events in the catheterisation laboratory. The study employed the TandemHeart\(^\text{®}\) (CardiacAssist Inc) device, which requires transseptal implantation and the use of two large cannulas that take time to implant. Fortuitously, the delayed reperfusion proved to be one of the critical components in translating acute unloading to the setting of AMI. The study used a closed chest swine model, again replicating typical events in the catheterisation laboratory. In the MI group \((n=4)\), MI was induced by occlusion of the left anterior descending (LAD) artery for 120 minutes, followed by 120 minutes of reperfusion without mechanical support. In the mechanically-supported group (MI plus unload; \(n=4\)), percutaneous left atrial-to-femoral artery bypass was initiated after 120 minutes of ischaemia, and LAD artery occlusion was prolonged for an additional 30 minutes, followed by 120 minutes of reperfusion with device activation timing but also investigated the concept of total and partial unloading. An early study in sheep found that if Impella is activated during reperfusion alone, the degree of unloading correlates with a reduction in infarct size.\(^6\)

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support. A significant reduction in infarct size was seen, which correlated with the reduction of LV stroke work.\(^1\)

An editorial, published alongside this article, posed a number of questions. First, is it clinically feasible to use devices requiring transseptal implantation in the setting of AMI? What is the optimal timing of delayed reperfusion? What was the mechanism responsible for the beneficial effects? These questions formed the basis of Dr Kapur’s next studies. At the time he had been studying the feasibility of left atrial unloading compared with LV unloading and concluded that the Impella provided the most effective unloading signature, giving a reduction in LV pressure and volume. In addition, the Impella device eliminated the need for transseptal puncture arterial access. A study was designed to test the hypothesis that initially reducing LV work and extending the delay to coronary reperfusion may limit myocardial injury in AMI. In the primary reperfusion group, the LAD artery was reperfused for 120 minutes. In the primary unloading group, after 90 minutes of ischaemia the axial flow pump was activated and the LAD artery left-occluded for an additional 60 minutes, followed by 120 minutes of reperfusion. There was a significant 43 % reduction in infarct size in the primary unloading group compared to primary reperfusion (73 ± 13 % versus 42 ± 8 %; p=0.005). There was a correlation between infarct size reduction and LV wall stress.

Another interesting finding was that unloading activates biological cardioprotective processes, increasing myocardial levels of the chemokine stromal cell-derived factor (SDF)-1 alpha, and that the regression plot of infarct size against SDF-1 alpha levels in the myocardium was almost linear (R=0.89; p<0.01; see Figure 2).\(^9\) This study led to the mechanical conditioning hypothesis: first unloading the LV, then delaying reperfusion activates a cardioprotective programme that limits myocardial damage in AMI (see Figure 3).\(^9\)

This hypothesis prompted further questions: how important is the delayed reperfusion? How important is the role of the kinases (i.e. is the mechanism primarily haemodynamic or biological)? What is the long-term effect of this intervention on LV recovery? Dr Kapur’s team is addressing these questions in a number of ongoing studies. In one currently unpublished study, a series of animals were divided into groups with ischaemia reperfusion alone or a delay in reperfusion after activating the Impella device of 15, 30 and 60 minutes. In the final group, the impella device was activated after balloon reperfusion. Results showed that 15–30 minutes of primary unloading was required to achieve infarct size reduction. A further study investigated the biological mechanisms for this finding and found that delayed reperfusion is required to activate cardioprotective signaling involving SDF-1 alpha. In another set of studies, following occlusion of the LAD artery, C-X-C chemokine receptor type 4 inhibitors (which inhibit SDF-1 alpha influx) or kinase inhibitors were administered. Both interventions increased the infarct size, demonstrating that...
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Figure 5: The Effect of Primary Unloading on Apoptosis

** Figure 6: Changing the Paradigm in the Management of Acute Myocardial Infarction

Quantitative polymerase chain reaction confirmed the expression of select genes from regulated pathways. Scanning electron microscopy evaluated mitochondrial integrity within infarct zones. Sham operated LV samples were used as controls.

Consistent with previous studies, primary unloading reduced infarct size compared to reperfusion alone, from 65% to 34%. Gene expression analysis yielded a heat map representing the 2,200 genes significantly regulated by primary reperfusion or primary unloading (p<0.01). A significant shift in gene expression was seen: the primary unloading group showed a heat map similar to the sham controls. The investigators then identified a number of key regulatory pathways altered by primary unloading, including inflammatory and fibrotic pathways. Specifically, matrix metalloproteinases MMP2 and MMP9 were upregulated in the reperfusion group and downregulated in the unloading group. MMP2 and MMP9 are involved in the breakdown of extracellular matrix, leading to adverse remodelling, and are markers of inflammatory response.

In the reperfusion group, there was increased expression in SMAD3, an intracellular signal transducer and transcriptional modulator that, following mechanical stretch, is phosphorylated by transforming growth factor-beta, and then converts fibroblasts to myofibroblasts, increasing adverse remodelling. Expression of genes in the electron transfer chain, which is responsible for adenosine triphosphate synthesis and other important pathways involved in cellular metabolism, was decreased in the reperfusion group compared with the unloading and sham groups, suggesting that unloading preserves the integrity of the electron transfer chain during AMI.

Finally, examination of mitochondrial integrity revealed a significantly increased number of intact mitochondria per cardiac myocyte in the unloading versus reperfusion group. Since mitochondrial function is linked to apoptosis, key components of the apoptotic pathway were examined. A higher density of the pro-apoptotic active BAX protein and procaspase-3 were seen in the reperfusion group, whereas higher densities of degraded, inactive, BAX and caspase-3 were seen in the sham and unloading groups. Higher levels of antiapoptotic agents B-cell lymphoma 2 and B-cell lymphoma–extra large were identified in the unloading group (see Figure 5).

In summary, this study identified for the first time that primary unloading triggers a global shift in gene expression within the infarct zone.

Young Investigator Scholarship Presentation

Michele Esposito, a member of Dr Kapur’s research team, presented the abstract that won the Young Investigator Scholarship awarded by the A-CURE Working Group. This study tested the hypothesis that primary unloading promotes myocardial salvage in AMI through regulation of gene expression within the infarct zone. The LAD artery of male pigs (n=4/group) was occluded for 90 minutes. In the primary reperfusion group, the LAD artery was reperfused for 120 minutes. In the primary unloading group, after 90 minutes of ischaemia a mechanical circulatory support device was activated and the LAD artery left-occluded for an additional 30 minutes, followed by 120 minutes of reperfusion. Myocardial infarct size was quantified by triphenyl tetrazolium chloride staining. Whole-transcript expression analysis was performed using a porcine microarray platform.

loss of kinase function attenuates the cardioprotective effect of primary unloading. In the final study, SDF-1 alpha was administered via intracoronary delivery to try to augment its cardioprotective effect. However, it was not possible to further reduce the infarct size by this method.

The final question – does acute unloading impact LV recovery? – was answered in a study with a 28-day follow-up period. In the primary reperfusion group, the infarct scar at 28 days was significantly larger than that in the primary unloading group. In terms of function, the primary reperfusion group showed a characteristic LAD artery infarct pattern whereas the primary unloading group showed primarily intact myocardium. Preliminary data (n=3) showed significant reductions in LV scar (see Figure 4).

In summary, there is a point at which the injury clock can be stopped and a protective process initiated that will limit the damage once reperfusion begins. This is the focus of Dr Kapur’s future work.
zone that is associated with preserved mitochondrial integrity and cellular respiration, reduced apoptosis, inflammation and fibrosis during the acute phase of MI. These data suggest that unloading the left ventricle and delaying reperfusion promotes cardioprotective signalling and may be a novel approach to limiting myocardial damage during AMI and preventing the subsequent development of ischaemic heart failure.

Dr Kapur concluded by stating that the burden of ischaemic heart failure will grow and that new approaches to cardioprotection in AMI are needed. Primary unloading reduces infarct size through a two-pronged approach: first by reducing the waveform of MI and second by activating a cardioprotective process (see Figure 6). However, prospective randomised controlled studies are required to test the clinical validity of these preclinical findings.


Cardiac Unloading and Recovery in Cardiogenic Shock: From Disease Modelling to Real Patients

Presented by Patrick Hunziker

Medical Intensive Care Unit and Cardiology, University Hospital Basel, Switzerland

Professor Patrick Hunziker began by discussing the need for and limitations of evidence-based medicine. While it is established that the strongest evidence for a therapeutic intervention is obtained from a systematic review of randomised controlled trials involving a homogeneous patient population, each human is unique. There are more potential human phenotypes than atoms in the universe. Similarly, the risk factors for cardiovascular disease are so numerous that it is impossible to produce an algorithm for assessing risk in clinical practice. In addition, acute myocardial infarction (AMI) is a disease that changes over time and is a different disease even after 3 hours. Considering these factors, the conventional requirements of a clinical trial (i.e. a homogeneous patient population) do not exist.

There is a need for knowledge-based, individualised medicine with an emphasis on an interdisciplinary approach. We must focus on and learn from individual patients, employing personalised treatment modalities, and adapt treatment regimens on a case-by-case basis. In AMI, our priority should be the avoidance of death and minimising myocardial necrosis through improved hospital management, the use of percutaneous coronary intervention (PCI) in unstable patients and the management of cardiogenic shock (CS).

Prof Hunziker has implanted around 300 Impella® (Abiomed) devices and provided practical insights from his experience of using bedside simulations. The first case was of a patient in severe arrhythmia. The mean arterial pressure (MAP) was zero. The use of an intra-aortic balloon pump had no effect on MAP; however, the use of the Impella raised the MAP to 55 mmHg (see Figure 1). The same patient subsequently experienced sudden complete atrioventricular block. By using the Impella 2.5 in this patient, MAP was maintained at 60 mmHg. In the second case, a patient presented with profound left ventricular (LV) failure. Combining mechanical support and vasodilators proved effective in this patient, and had a beneficial effect on oxygen consumption. In both cases, mechanical support by the Impella gave the physician the advantage of restoring MAP (and perfusion pressure), even in the absence of cardiac function.

There is a need to optimise the use of mechanical circulatory support (MCS) devices in routine clinical practice. One paradigm currently under investigation is the combined use of MCS and vasodilators in order to optimise organ perfusion in CS, as well as minimising LV wall stress and LV work. A LV assist device (Impella) is employed first, followed by the administration of vasodilator drugs (nitrates or angiotensin-converting-enzyme inhibitors) with a target MAP of 65 mmHg (see Figure 2).

In order to further develop the use of the Impella in CS, there is a need for improved monitoring and a willingness to change approaches based on haemodynamic data. The most important factor in the treatment of CS is time; early haemodynamic support is essential to avoid a systemic inflammatory response. Operator speed is crucial and increases with experience. It is feasible that implantation time
may be reduced to 1–2 minutes in the future. However, it is also vital to optimise treatment decisions by correctly incorporating the use of the Impella device within current treatment algorithms.

While it may be easy to identify CS, deciding in which patients we should delay reperfusion is less straightforward. Figure 3 shows an algorithm proposed by Prof Hunziker for the treatment of patients presenting with AMI and CS. This algorithm highlights the heterogeneity within both the patient population and the treatment of AMI itself. In selecting patients to undergo Impella implantation, it is useful to consider the potential for brain stem recovery if patients are supported early and given adequate therapies.

This presentation sparked a debate about whether current evidence was sufficient to provide haemodynamic support at small centres. Around 60% of cases of CS are treated at small centres in the US, with a potential delay caused by patient transportation to a larger centre. In many cases, some form of advanced haemodynamic support might allow these sites to either reperfuse more safely on site and/or facilitate the safer transfer of these patients to expert facilities. The question was raised as to whether all primary PCI centres should be mandated to Impella. The consensus opinion was not at this time but perhaps this will develop over the coming years. Prof Hunziker strongly encouraged centres with primary PCI capability to start MCS on site but to be in close communication with a central hub. There was a recognised lack of sufficient evidence to indicate that MCS be initiated in these centres followed by patient transfer. Problems relating to geography may become an important factor, as journey times to a central hub may be long in some regions.

Prof Hunziker concluded by observing that the A-CURE symposium provides an excellent platform for future progress towards new paradigms in AMI and cardiopulmonary resuscitation. The use of modelling and monitoring will enable the optimal use of new technologies for personalised disease management.

Keynote Speech
Heart Failure: The Path Ahead

Presented by Joseph A Hill
UT Southwestern Medical Centre, Dallas, TX, USA

Joseph Hill is a Professor in the Department of Internal Medicine’s Division of Cardiology and the Department of Molecular Biology at UT Southwestern Medical Center and is the Chief of Cardiology and Director of UT Southwestern’s Harry S Moss Heart Center. He is the current Editor-in-Chief of Circulation.

Professor Hill’s presentation placed the concept of myocardial unloading into the broader topic of heart failure (HF), a growing clinical, economic and social problem due to its increasing incidence and poor prognosis. At present we cure very few diseases but instead turn acute disease into chronic disease, which we manage progressively. Thanks to numerous clinical advances in the management of acute myocardial infarction (MI), in-hospital mortality has fallen substantially, from 30 % in the 1960s to around 2–3 % today, and we are moving into an era of lifelong disease management.1 The decreased mortality from cardiovascular disease is impressive when compared to other diseases. The decline in age-adjusted mortality in relation to scientific advances is 75 % (see Figure 1); by comparison, the reduction for cancer is 10 %.1 However, this reduction in MI mortality has been accompanied by an increased incidence of HF2–3 and thus, despite these successes, cardiovascular disease remains the leading cause of death worldwide. There is a need to halt the rise in HF incidence. This has led to an upsurge in interest in mechanical circulatory support devices, which form the focus of the symposium.

A major cause of HF is cardiac remodelling due to hypertrophic growth, the primary mechanism by which the heart reduces stress on the ventricular wall. The heart is a remarkably plastic organ and can grow by up to 50 % under different circumstances including exercise and pregnancy, but also in pathological conditions such as hypertension and infarction.4 These changes can occur rapidly. The heart can also atrophy by up to 70 % in situations such as the use of implantable ventricular assist devices, cancer and bed rest.4 Factors contributing to remodelling include elevated preload, ischaemia, metabolic and neurohumoral factors. One signalling pathway known to be responsible for disease-related plasticity involves class I and II histone deacetylases (HDACs). If a heart is exposed to thoracic aortic constriction to increase afterload, it will grow by about 40 %. If the heart is then exposed to a broad-spectrum inhibitor of HDACs, the growth response is halved, suggesting that some of the growth is HDAC-dependent.5 HDAC inhibitors can also reverse pathological cardiac hypertrophy and restore cardiac function by suppressing autophagy.5

Another example of myocardial plasticity focuses on metabolic stress due to the deterioration of healthy lifestyles.2 Obesity trends in the US over the past 25 years show astounding changes in prevalence. In 1995, all US states had obesity rates >10 %. By 2000, only one state had obesity rates <15 % and rates of 20–24 % emerged. By 2005 we saw the emergence of obesity rates >30 %. By 2010, all states had obesity rates of at least 20–24 %.6 These trends in obesity are now being seen worldwide and are accompanied by the rising prevalence of diabetes. It is

Figure 1: Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances

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Figure 2: The Role of Foxo1 in Diabetes-related Cardiovascular Disease

Cardiomyocyte
- FOXO
- Diabetic Cardiomyopathy
- IROS
- PPARα
- Altered Ca2+
- Altered metabolism
- I RS
- Angiogenesis
- I CERK
- PKC
- I Ceramides
- I AGEs
- I RAAS
- I Cytokines

Cardiomyocyte

AGES = advanced glycation end products; Ca = calcium; PPAR = peroxisome proliferator-activated receptors; PKC = protein kinase C; RAAS = renin-angiotensin-aldosterone system

Figure 3: Promising New Interventions in Cardiovascular Disease

ASSIST
- Percutaneous assist devices
- Ventricular assist devices

MODULATE
- Autonomic nervous system
- Neurohumoral pathways

REPLACE
- Total artificial heart

REPROGRAMME
- Fibroblast transdifferentiation

REPAIR
- Fibroblast
- Cell-based therapies
- Tissue engineering

MRA = magnetic resonance angiogram. Source: Udeshion and Stevenson, 2016

Another growing public health problem is HF with preserved ejection fraction (HFpEF). HFpEF occurs in 40–60 % of newly-diagnosed HF cases, has an annual mortality of 3–30 % and accounts for a healthcare expenditure of more than $20 billion in 2010. In contrast to HF with a reduced ejection fraction, patients with HFpEF still do not benefit from evidence-based treatment options. It remains one of the most challenging clinical syndromes because there are no reliable preclinical models and so it is impossible to develop new therapies. None of the currently-available therapies have shown improved clinical outcomes in trials of HFpEF and these patients’ prognosis has remained unchanged over the past 15 years. This is partly due to the numerous proposed pathophysiological mechanisms underlying the condition, which involve multiple organs. If current trends persist, HFpEF will spread into the developing world and be responsible for 7.8 million premature cardiovascular disease (CVD) deaths in 2025. In addition to this, the costs of CVD, both direct and indirect, are projected to increase substantially.

Despite the challenge ahead, Professor Hill ended on a note of optimism. A number of new interventions for CVD appear promising (see Figure 3). Projections have shown that National Institutes of Health funding translates into improvements in CVD mortality. Furthermore, opportunities lie in the field of genetics. It has been hypothesised that cardiomyocyte-specific Foxo deletion will sustain cardiac function in the setting of insulin resistance. By focusing on the molecular basis of diabetes, we have the potential to mitigate the projected healthcare cost of this growing epidemic. Finally, as highlighted by other presentations at the A-CURE symposium, mechanical unloading can minimise the infarct size and thus has the potential to reduce the incidence of HF.
Cardiac Unloading and Myocardial Recovery: Clinical Utility from a Surgeon’s Perspective

Presented by Mark Anderson

Hackensack University Medical Center, Philadelphia, PA

Mark Anderson was previously the Chair of the Cardiothoracic Surgery at Einstein Medical Center in Philadelphia. Dr Anderson specialises in the surgical management of heart failure and myocardial recovery.

Dr Anderson gave a surgeon’s perspective on cardiac unloading. He commenced by reminding the congress that cardiopulmonary bypass is the foundation of cardiac support. By placing the patient on bypass, the heart is completely unloaded, allowing the surgeon to conduct the necessary procedure. However, while more patients are surviving following acute myocardial infarction (AMI), evidence indicates that heart function is not being necessarily recovered. This increased survival rate with insufficient heart recovery is leading to more hospital admissions and an increased rate of heart failure.

Mechanical circulatory support (MCS) is increasingly being recognised as a valuable intervention in AMI. The US Food and Drug Administration states that: “The Impella 2.5, Impella CP, Impella 5.0 and Impella LD catheters, in conjunction with the Automated Impella Controller console, are intended for short-term use (≤4 days for the Impella 2.5 and Impella CP and ≤6 days for the Impella 5.0 and Impella LD) and indicated for the treatment of ongoing cardiogenic shock (CS) that occurs immediately (<48 hours) following AMI or open heart surgery as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures with or without an intra-aortic balloon pump. The intent of the Impella system therapy is to reduce ventricular work and to provide support necessary to allow heart recovery and early assessment of residual myocardial function.” This statement emphasised the potential for the Impella® (Abiomed) pump in heart recovery and established a role for surgery in MCS.

Following the availability of these powerful new interventions, clinicians need guidance on how to optimise their use. Table 1 shows the factors that should be considered when choosing the level of support in haemodynamic deficit and when surgery is needed. Another tool that can help in clinical decision-making is cardiac power output, a potent indicator of mortality.1 Interventions can be targeted on the basis of early cardiac power output and subsequently assessed. Full unloading can optimise recovery, but there is a need to meet the demands for increased unloading and support. The early decision to both initiate and escalate MCS is particularly important in optimising outcomes. The Impella 5.0 is the most commonly used device for escalation in current surgical clinical practice.

There is also a need for more clinical evidence to guide the use of these devices. Since large randomised clinical trials involving cardiogenic shock patients are difficult to conduct, the global catheter-based Ventricular Assist Device Registry™ has been created.2 Its purpose is to capture data reflecting real-world use of Impella devices in current clinical practice and provide insights into patient characteristics, co-morbid conditions, outcomes, patterns of care and the performance metrics of participating institutions to guide improvement in ventricular assist device use. Data from the registry show that surgical devices are still needed in advanced cases. Percutaneous technology is still associated with disadvantages, including instability of femoral artery placement and the restriction of the patient being confined to bed to recover. Axillary artery implantations allow for patient mobility and a more rapid patient recovery.

The use of ventricular assist devices in AMI complicated by cardiogenic shock has a number of advantages: it completely rests the heart, reduces the need for inotrope/pressor support and provides stability during acute events. It is an effective bridging strategy and an optimal recovery platform. In order to optimise its use in routine clinical practice, there is a need for collaboration between interventional cardiologists and surgeons.

Dr Anderson finished by highlighting the need for a standard treatment algorithm and presented an algorithm that has proven effective in his centre (see Figure 1). He concluded that this meeting has demonstrated some important paradigm shifts in the management of cardiogenic shock, from partial unloading to optimal unloading; from later referral to early escalation; univentricular MCS to biventricular MCS; and the concept of a bridge to recovery rather than to a transplant.

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Table 1: Haemodynamic Deficit: Considerations for the Treatment of Cardiogenic Shock

<table>
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<tr>
<th>Haemodynamic Burden</th>
<th>EF %</th>
<th>SBP</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>74</th>
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Green: <2.0 L/min Impella 2.5; orange: 2–4 L/min Impella CP/5.0; red >4.0 L/min Impella 5.0/LD. Orange and red: consider surgical options.

BSA = body surface area; EF = ejection fraction; SBP = systolic blood pressure.
Acute Unloading in the Setting of Acute Myocardial Infarction Complicated by Cardiogenic Shock

Dr William O’Neill is the Medical Director of the Henry Ford Health System and pioneered the use of angioplasty in heart attack treatment. In the field of structural heart disease, he performed the first transcatheter aortic valve replacement procedure in the US in 2005. He has received numerous awards and has authored more than 300 peer-reviewed articles and abstracts.

Dr O’Neill began his presentation by highlighting the need for improved outcomes in cardiogenic shock (CS). Mortality in CS used to be as high as 90% in the 1960s. Thirty years ago, the first studies reporting the outcomes of angioplasty for CS were published. Results showed a survival rate of 50%. Survival has not improved since then. A recent cohort study found that long-term outcomes in CS remain poor. This represents a clear, unmet need.

While the advent of mechanical circulatory support (MCS) devices offers promise in terms of improving outcomes in CS patients, there is a need for more evidence in support of their use. The catheter-based Ventricular Assist Device Registry™ (cVAD Registry™) is a global observational clinical registry designed to monitor patient safety and real-world outcomes of patients supported with the Impella® (Abiomed) device. Dr O’Neill presented registry data from his patients who were in severe hemodynamic compromise. These data showed that the use of increasing numbers of inotropes prior to MCS implantation is associated with worse survival and may increase the size of an infarct.

The time between onset of CS and initiation of MCS is also an important determinant of survival. Figure 1 shows in-hospital survival rates as a function of the time interval between onset of CS and initiation of MCS.

Incorporating Infarct Size into Composite Endpoints

Incorporating Infarct Size into Trial Composite Endpoints: Implications for Unloading Trials

Presented by James E Udelson
Division of Cardiology, CardioVascular Center, Tufts Medical Center, Boston, USA

Dr James Udelson is the Chief of the Division of Cardiology as well as the Director of Nuclear Cardiology at Tufts Medical Center. Dr Udelson’s research interests involve new therapeutic modalities in the setting of heart failure as well as chronic coronary artery disease.

Dr Udelson began his presentation by highlighting the problems of clinical trials enrolling heart failure (HF) patients. Clinical trials are extremely expensive and the majority of patients do not contribute to the primary endpoint. This is demonstrated in contemporary clinical trials in HF, where event rates are usually low. In the recent Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, the 1-year rate of cardiovascular death/hospitalisation was 10–12 %; therefore, in order to demonstrate statistical significance,
the trial needed to enrol >8,000 patients. In the 2012 Abciximab Intracoronary versus intravenous Drug Application in ST-elevation myocardial infarction (AIDA STEMI) trials, a three-point composite endpoint was used, but despite recruiting >2,000 patients, the trial had an event rate of only 7 % at 90 days and statistical significance was not achieved.2

As the use of cardiac unloading moves into less severely ill patients, such low event rates will become an issue in trial design. There is therefore much interest in biomarkers as surrogates in trials. A marker considered a surrogate when it is in the causal path between the remedy and the outcome. Markers may be serum biomarkers, such as troponins or natriuretic peptides, or imaging biomarkers, such infarct size, left ventricle volume and ejection fraction. All intervention effects pass through the marker in the causal path or are captured by the marker.

Dr Udelson focused on the use of infarct size measured by cardiac magnetic resonance (CMR) imaging as a plausible marker for myocardial infarction (MI). A large body of data shows that infarct size influences established clinical outcomes such cardiovascular death and HF hospitalisation. However, therapeutic intervention-induced changes in the surrogate marker need to be reflected in changes in the clinical outcome. At present, no marker is able to achieve this standard. Biomarkers that are ‘prognostic’ are not necessarily good surrogate markers in terms of assessing the effects of therapy. As an example, premature ventricular complexes following MI are strongly associated with an unfavourable prognosis. However, in the Cardiac Arrhythmia Suppression Trial (CAST), suppression of premature ventricular complexes led to an increased mortality. Likewise, low high-density lipoprotein is prognostic of an increased risk of incident coronary artery disease, but the use of the cholesteryl ester transfer protein inhibitor torcetrapib to raise high-density lipoprotein levels increased mortality due to its effects on glucose, insulin and HbA1c in subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial.3

The question of whether infarct size is an appropriate surrogate endpoint was addressed in a recent study by Dr Udelson’s research team: a pooled patient-level meta-analysis from 10 randomised primary percutaneous coronary intervention in ST-elevation MI trials (n=2,632 patients) in which infarct size was assessed within 1 month after randomisation by either CMR imaging or technetium-99m single-photon emission CT, with clinical follow-up for ≥6 months. A strong correlation was seen between infarct size (per 5 % increase) and subsequent mortality (1.19, 95 % CI [1.18 to 1.20]; p<0.0001) and hospitalisation for HF (adjusted hazard ratio: 1.20; 95 % CI [1.19–1.21]; p<0.0001), independent of age, sex, diabetes, hypertension, hyperlipidaemia, current smoking, left anterior descending versus non-left anterior descending infarct vessel, symptom-to-first device time and baseline thrombolysis in MI flow 0/1 versus 2/3. Infarct size was not significantly related to subsequent reinfarction. For every 1 % reduction in infarct size, there was a 16 % reduction in HF hospitalisation but no effect on all cause mortality. The investigators plan to meet with the US Food and Drug Administration (FDA) to discuss whether these data support the incorporation of infarct size into trial outcomes.

If the FDA approves the use of infarct size as a surrogate endpoint in clinical trials, the next challenge will be how to incorporate it. Two methods may be useful: the Finkelstein–Schoenfeld method and the ‘win ratio’, which involve a hierarchical comparison of events/timing in pairs of patients from the groups in the trials. The analyses account for clinical priority (e.g. death is more important than HF hospitalisation) and allow the potential incorporation of longitudinal measures such as the change in 6-minute walk distance or biomarkers. Most importantly, these methods enable all patients in a trial to contribute to the endpoint.

Dr Udelson illustrated this concept by considering a hypothetical randomised controlled ST-elevation MI trial that investigates cardiac unloading. Group A comprises 100 patients who receive unloading, while group 2 comprises 100 controls (see Figure 1). The investigator takes a patient (e.g. patient 1) from group A and another (e.g. patient 22) from group B and compares them. At the first level of hierarchy, the investigator compares whether either patient died. If B22 died but A1 was alive at study completion, then A ‘wins’ that comparison. If both patients died but A1 died at 12 months while B22 died at 8 months, then group A ‘wins’. However, in HF or acute MI trials, most patients do not die. The following step is to consider the next level, i.e. HF hospitalisations. If B22 was hospitalised but A1 was not, then group A ‘wins’. In ST-elevation MI, neither of these events may occur so it may be necessary to move to a marker with a plausible relationship with outcomes. If A1 has an infarct size of 5 % but B22 has an infarct size of 12 %, then group A ‘wins’ that comparison. If each person in group A is compared in this way with each person in group B, we obtain 10,000 comparisons.

This approach is familiar to the FDA. It was used in cohort B of the transcatheter aortic valve replacement group in the Placement of AoRtic TranScathetEr Valves (PARTNER) trial, which had co-primary endpoints of all-cause mortality (p<0.0001 favouring the device) and a hierarchical composite of death/recurrent hospitalisation, analysed by the Finkelstein–Schoenfeld method. Results showed superiority of the device (p<0.0001). Dr Udelson concluded that incorporating validated markers into hierarchical composites may allow reasonable sample sizes for trials of approaches to ST-elevated MI such as mechanical circulatory support.
Summary of Presentations Exploring Other Aims of the A-CURE Group

The A-CURE Working Group also aims to explore the potential limitations of applying acute unloading in the clinical setting. One of these limitations may be found in data from Professor Michael Cohen of the University of South Alabama, which suggests that many patients being treated for acute myocardial infarction (MI) come into the clinic with the preconditioning signalling cascades already activated due to the wide use of P2Y12 inhibitors. Many experimental therapies look to exploit these same signalling cascades for therapeutic purposes. If these signals have already been activated in the patients, then experimental therapy will have a limited effect. Professor Cohen concluded that in all preclinical models of ischaemia/reperfusion, any intervention being investigated for its cardioprotective qualities must be evaluated in the presence of P2Y12 blockade to determine whether the second intervention’s protection is additive to that of currently indicated anti-platelet agents.

Dr Ryan Tedford, Assistant Professor of Medicine at Johns Hopkins School of Medicine, gave a presentation on the use of mechanical support for right-sided and biventricular failure. Even patients with chronic right ventricular (RV) failure respond to reductions in afterload. Clinical data suggest that, despite reducing RV load, left ventricular assist device (LVAD) implantation initially worsens the RV adaptation to load. However, continued LVAD support results both in improved RV afterload and RV adaptation as the load decreases, and the relationship between these two remains constant over time. RV mechanical circulatory support can be initiated early or later in the treatment of RV failure. Data comparing the benefits of primary versus delayed support have been mixed. A 2009 study found that early implantation of biventricular devices was associated with better outcomes compared to delayed implantation, suggesting that the timely implantation of a primary RV assist device is potentially beneficial. A separate study found that temporary RV mechanical circulatory support is an acceptable way to manage postoperative RV failure and that this is preferable to biventricular support. In most cases, and in the setting of contemporary LVADs, temporary RV support and optimisation of RV load may be sufficient.

Professor Derek Hausenloy of Duke-National University of Singapore discussed the challenges of reducing infarct size following acute MI. The most promising future interventions to limit MI scar size each require application prior to percutaneous coronary intervention (PCI) in order to maximise their effects. This observation aligns with data surrounding the ability of acute unloading to limit MI scar size. It has been shown that applying the glucagon-like peptide-1 agonist exenatide prior to PCI, metoprolol prior to PCI, or remote ischaemic conditioning prior to or at the time of PCI may each limit MI scar formation. Professor Hausenloy concluded that new techniques such as unloading and newer therapeutic targets and strategies should further improve outcomes.
Summary and Concluding Remarks

Following the presentations, the panel summarised some of the key points raised at the meeting. It is evident that clinical trials for mechanical circulatory support pose challenges that are in part mechanistic but also related to trial design. If we can reduce the cost of how we screen and enrol patients, we may allow for better evaluations of new devices and interventions, with definitive answers at the conclusion of the trial. Clinical studies in the setting of cardiogenic shock are challenging to execute, but there is a need for data.

One of the key messages of the session was there is no one size fits all approach and we should be thinking of individualised rather than broad treatment plans. Moving forward, we now have an amazing tool that can provide haemodynamic support and avoid the use of vasopressors. However, some patients may still need vasopressors or inotropes. In these cases, the use of additional haemodynamic support will dramatically decrease morbidity.

The management of acute myocardial infarction and chronic heart failure (HF) present different challenges. In the future, A-CURE may split into two groups: one focused on acute myocardial infarction and the other on chronic HF, since acute unloading will have very different effects on the two states. We need to establish the precise nature of these differences before contemplating a split. In the chronic HF setting, there is a need for a balance between left and right ventricular support. The right ventricle is dependent on the left ventricle for function, so any support for the right ventricle must not indirectly impact left ventricular function. More studies are needed in the chronic HF setting.

In terms of acute unloading, compelling evidence has been presented in favour of delaying reperfusion in order to provide mechanical circulatory support, but before moving this approach into the clinic, caution was advised; the priority should be to ensure robust protection for the patient, and delaying reperfusion for up to half an hour may not be feasible in all cases. More clinical evidence is needed to support this intervention. We need to strive for definitive answers to whether cardiac unloading is beneficial and not rely on subanalyses of clinical trials. Finally, the fields of chronic and acute unloading are merging and the focus on oxygen supply rather than demand is a fascinating approach.

Dr Kapur closed by stating that this had been a ground-breaking meeting and acknowledged support in the form of sponsorship from Abiomed.

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